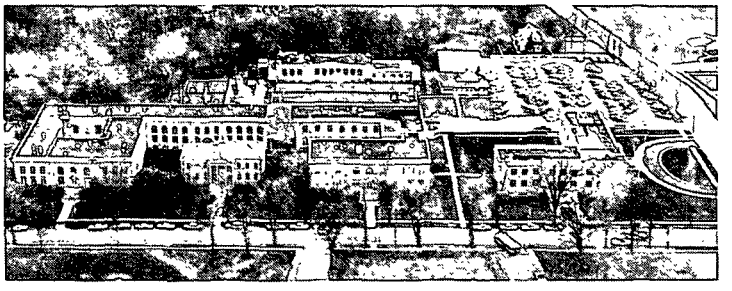

THE INSTITUTE OF PAPER CHEMISTRY, APPLETON, WISCONSIN

IPC TECHNICAL PAPER SERIES
NUMBER 144

SYNTHESIS OF 1,5-ANHYDROALDITOL PERACYLATES

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AUGUST, 1984

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ABSTRACT

1,5-Anhydroalditol peracetates or perbenzoates were conveniently prepared in good yield (>65%) by Raney nickel (W-5) reduction of α-glycopyranosyl bromide peracylates.

DISCUSSION

We have used 1,5-anhydroxylitol (**1**) and 1,5-anhydroribitol (**2**) to investigate degradation of pyranoid rings by oxygen in alkaline media.[1] We have also used 1,5-anhydro-D-glucitol (**3**), 1,5-anhydro-4-O-β-D-glucopyranosyl-D-glucitol (**4**) and 1,5-anhydro-4-O-α-D-glucopyranosyl-D-glucitol (**5**) in studies of glycosidic bond cleavage under alkaline conditions.[2,3] Continuation of these studies has necessitated preparing substantial quantities of these and other 1,5-anhydroalditols.

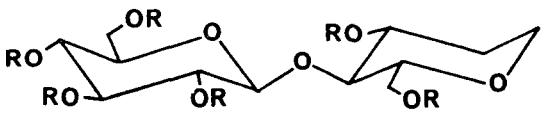
Syntheses of anhydroalditols have been reviewed.[4,5] Esterified 1,5-anhydroalditols have been prepared by palladium- or platinum-catalyzed hydrogenation of esterified glycopyranosyl halides in the presence of amines,[1,2,6-10] sodium borohydride reduction of the esterified glycopyranosyl nitrates[11] or reductive desulfuration of esterified 1-thioglycopyranosides with Raney nickel.[1,3,12-14] More recently, 1,5-anhydro-D-hexitol peracetates were prepared by reduction of D-glycopyranosyl chloride[15] or bromide[16] peracetates with tributylstannane. Reduction of esterified

glycopyranosyl halides with lithium aluminum hydride yields the 1,5-anhydroalditols due to concomitant deesterification.[2,17-19] Reductive cleavage of permethylated alkyl glycopyranosides or polysaccharides with boron trifluoride etherate or trimethylsilyl trifluoromethanesulfonate as the cleavage catalyst and triethylsilane as the reducing agent yields the corresponding methylated 1,5-anhydroalditol.[20,21]

Until recently we have preferred Raney nickel-desulfuration of esterified phenyl 1-thioglycopyranosides for large scale preparation of 1,5-anhydroalditol peracylates because of good yields and ease of product isolation.[1,3] However, since the thioglycosides are typically synthesized from glycosyl halides, reduction of the glycosyl halide has the obvious advantage of one less synthetic step. We now report syntheses of the peracetates of **1**, **3**, **4**, **5**, and 1,5-anhydro-D-mannitol (**6**) by Raney nickel-reduction of the α-glycopyranosyl bromide peracetates of D-xylose, D-glucose, cellobiose, maltose, and D-mannose, respectively. Similarly, the tribenzoate of **2** was prepared by Raney nickel-reduction of 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl bromide. The method appears to have general utility, and the acylated anhydroalditols which are formed in good yield (>65%) are easy to isolate from the product mixture. The only report of a similar reduction is a brief mention of reduction of tri-O-benzoyl-β-D-arabinopyranosyl bromide with Raney nickel as part of a study of the preparation of 2-deoxysugars by hydrogenolysis of benzoylated glycopyranosyl bromides.[9] The yield of 2-deoxysugar was only 3%, but the yield of 1,5-anhydro-tri-O-benzoyl-D-arabinitol was 52%.

As with palladium- or platinum-catalyzed hydrogenation of acylated glycopyranosyl halides[7,9] and Raney nickel-desulfuration of thioglycopyranosides,[3,22] mono- and dideoxy analogs of the 1,5-anhydroalditols are side products in Raney nickel-reductions of acylated glycopyranosyl bromides. However, these compounds, typically identified by GLC-MS, did not interfere with crystallization of the acetylated 1,5-anhydroalditols. In the reduction of

hepta-O-acetyl-α-cellobiosyl bromide, 3,6-di-O-acetyl-1,5-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-D-arabino-hexitol (7) was isolated and characterized.



7 R = Ac

13 R = H

EXPERIMENTAL

General

Melting points were determined on a calibrated Thomas-Hoover capillary apparatus. Optical rotations were determined with a Perkin-Elmer 141MC polarimeter. NMR spectra were obtained on a Jeol FX100 Fourier transform spectrometer at normal probe temp using TMS as an external standard.

TLC was performed on silica gel G (Merck D-5) using $CHCl_3$-EtOAC (10:1, vol) as the developing solvent. Residual glycopyranosyl bromide peracylate in the analytical sample was hydrolyzed to the reducing sugar with silver nitrate (3%) in acetone-water (19:1, vol) prior to TLC analysis. Components were detected by spraying the chromatograms with H_2SO_4 in MeOH (1:4, vol), followed by charring.

GLC was performed on a Perkin-Elmer Sigma 2 instrument equipped with a flame ionization detector. A column of OV-101 (3%) on Supelcoport (80-100 mesh) housed in stainless steel (5 ft. x 0.125 in. o.d.) and rigged for on-column injection was used. Nitrogen (30 mL min^{-1}) was used as the carrier gas. The operating conditions were: injector, 275°C; column, 130°C for 1.0 min, then 7°C min^{-1} to 275°C; and detector, 300°C.

A Hewlett-Packard 5985 instrument was used for chemical ionization GLC-MS. The GLC conditions were similar to those described

above except that a longer glass column (6 ft. x 0.125 in. o.d.) was used and methane was used as the carrier gas. The GLC-MS interface was maintained at 250°C., and the source at 200°C. An ionizing voltage of 230 ev was used.

Type W-5 Raney nickel was prepared from nickel-aluminum alloy (1:1, wt; Alfa Chemical) as described by Augustine[22,23] with the exception that tetrahydrofuran (THF) was substituted for EtOH.

2,3,4,6-Tetra-O-acetyl-1,5-anhydro-D-glucitol (**8**).

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide[24] (53.0 g) and triethylamine (10 mL) were dissolved in THF (350 mL). Raney nickel (119 g) was added to the solution and the mixture was stirred overnight at room temp. The reduction was monitored by TLC. The catalyst (pyrophoric when dry) was filtered, and cautiously washed with acetone (2 x 250 mL). The combined filtrates were concd in vacuo to a thick oil. Cryst of the oil from abs EtOH yielded **8** (33.7 g, 79%); mp 72-73.5°C and $[\alpha]_D$ + 38.7° ($CHCl_3$). Lit:[25] mp 73.6-74.8°C and $[\alpha]_D$ + 38.9° ($CHCl_3$).

The reduction was also performed in less volatile THF-EtOH (1:1, vol) without any reduction in yield or formation of discernable ethyl glucosides.

A minor amount of 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hexitol (**9**) [GLC retention 0.73 relative to (**8**)] was formed in the reduction as indicated by chemical ionization GLC-MS analysis [m/e 315 (1.0%, M + 41), 303 (1.2%, M + 29), 275 (13.2%, M + 1), and 215 (100.0%, M - 59)].

2,3,4-Tri-O-acetyl-1,5-anhydroxylitol (**10**).

Reduction of 2,3,4-Tri-O-acetyl-α-D-xylopyranosyl bromide[26] with Raney nickel as described for the preparation of **8** and cryst of the product from abs EtOH yielded (**10**) (66%); mp 121-122°C and $[\alpha]_D$ 0° ($CHCl_3$). Lit:[27] mp 122-123°C and $[\alpha]_D$ 0° ($CHCl_3$).

2,3,4,6-Tetra-O-acetyl-1,5-anhydro-D-mannitol (**11**).

D-Mannose pentaacetate, prepared by acetylating D-mannose

(9.9 g) with acetic anhydride and pyridine,[28] was converted to tetra-O-acetyl-α-D-mannopyranosyl bromide by treatment with HBr in HOAc.[24] The crude bromide was added to a slurry of Raney nickel (53 g) in THF (150 mL) and triethylamine (5.5 mL). The mixture was stirred for 24 h at room temp and then 6 h at 40°C, and filtered through celite. The nickel residue was rinsed with THF and the combined filtrates were concd in vacuo to an oil which on cryst from abs EtOH yielded **11** (9.25 g, 51% yield based on D-mannose), mp 63-65°C., $[\alpha]_D$ -41.2° ($CHCl_3$). Lit:[29] mp 66-67°C, $[\alpha]_D$ -42° ($CHCl_3$).

2,3,6-Tri-O-acetyl-1,5-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-D-glucitol (**12**).

Hepta-O-acetyl-α-cellobosyl bromide[2] (121 g) and triethylamine (10 mL) were dissolved in THF (800 mL). The solution was added to a slurry of Raney nickel (180 g) in THF-EtOH (350 mL, 1:1, vol). The mixture was stirred at 30°C for 30 min and then overnight at room temp. The slurry was filtered and the catalyst was rinsed with THF-EtOH (2 L; 1:1, vol). The filtrates were concd in vacuo to a solid which on cryst from abs EtOH yielded **12** (83.5 g, 78%), mp 194.5-195°C, $[\alpha]_D$ + 3.8° ($CHCl_3$). Lit:[2] mp 193.5-194°C, $[\alpha]_D$ + 4.1° ($CHCl_3$).

Minor amounts of 3,6-di-O-acetyl-1,5-anydro-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-D-arabino-hexitol (**7**) (GLC retention 0.93 relative to **8**) were formed in reductions of hepta-O-acetyl-α-cellobiosyl bromide as indicated by chemical ionization GLC-MS analysis [m/e 603 (3.1%, M + 41), 591 (5.9%, M + 29), 503 (5.3%, M - 59), 331 (100.0%, glycone)].

Several mother liquors remaining after cryst of **12** from the reduction products were concd in vacuo to a thick oil. Cryst of the oil from abs EtOH yielded **7**, which on recryst from abs EtOH had mp 132.5-133.5°C and $[\alpha]_D$ + 6.1° ($CHCl_3$).

Deacetylation of **7** with NaOMe in MeOH[30] and cryst of the resultant ppt from 95% EtOH yielded 1,5-anhydro-2-deoxy-4-O-(β-D-glucopyranosyl)-D-arabino-hexitol (**13**), mp 209-211°C and $[\alpha]_D$ + 3.7° (H_2O) (Found: C, 46.2; H, 7.2. $C_{12}H_{22}O_9$ requires C, 46.4; H, 7.1%). The ^{13}C-NMR spectrum (D_2O) had resonances at 33.4 (t,C-2), 61.7 (t, C-6 and C-6'), 66.3 (t, C-1), 70.6 (d, C-4'), 71.8 (d, C-3), 74.3 (d, C-2'), 76.7 (d, C-5'), 77.0 (d, C-3'), 80.0 (d, C-4), 82.2 (d, C-5), and 103.6 (d, C-1') ppm.

2,3,6-Tri-O-acetyl-1,5-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-D-glucitol (**14**).

β-Maltose octaacetate (40 g) [mp 156-158°C, literature mp 159-160°C[31]], prepared by acetylating maltose monohydrate with pyridine-acetic anhydride,[28] was converted to hepta-O-acetyl-α-maltosyl bromide by treatment with HBr in HOAc.[32] Reduction of the crude maltosyl bromide with Raney nickel as described for the preparation **12**, and cryst of the product from abs EtOH yielded **14** (25.6 g, 70% based on maltose octaacetate), mp 132.5-134°C, $[\alpha]_D$ + 81.5° ($CHCl_3$). Lit:[33] mp 133-134°C, $[\alpha]_D$ + 82.0° ($CHCl_3$).

1,5-Anhydro-2,3,4-tri-O-benzoyl-ribitol (**15**).

Triethylamine (2 mL) and 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl bromide[34] (2.40 g) were added to a slurry of Raney nickel (10 g) in THF (60 mL). The mixture was stirred at room temp for 21 h. The Raney nickel was filtered, and rinsed with THF (2 x 150 mL). The combined THF solutions were concd *in vacuo* to a thick oil which on cryst from MeOH yielded **15**; (1.33 g, 66%) mp 156-158°C, $[\alpha]_D$ 0° ($CHCl_3$). Lit:[34] mp 156-157°C, $[\alpha]_D$ 0° ($CHCl_3$).

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